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Research Article

ENHANCEMENT OF ENTACAPONE BIOAVAILABILITY BY POLYMORPHISM

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Aim: Enhancement of Entacapone Bioavailability by Polymorphism.

Materials & Method: Entacapone Pure was obtained from IPCA Laboratories. Bhopal, India. The various solvents used for preparation of crystals were Acetone, Acetonitrile, Acetic acid, Ammonia, Benzene, Chloroform, Di-methyl sulfoxide, (Chempure Laboratories, Chennai), Dimethylformamide, Dichloromethane, Distilled water, Ethanol, Isopropanol, and Methanol (Reachem Laboratories Chem.Pvt.Ltd.Chennai).

Results: All the four forms of crystals (Form I, II, and III & IV) were prepared, characterized by using SEM analysis, DSC, FTIR and XRD studies. Above the crystals were formulated and evaluated its dissolution profile.

Conclusion: From the above results formulation Form IV crystals of Entacapone has shown greater and faster dissolution profile.

Key Words: Entacapone, polymorphs, SEM Analysis, DSC, XRD, IR.

1. Introduction

The present study enlightens to enhance the bioavailability of Entacapone which comes under BCS Class-IV drugs. Entacapone is a selective, reversible catechol-o-methyl transferase (COMT) inhibitor used for the treatment of Parkinson's disease which is insoluble in water. By considering this property we made an attempt to improve the solubility and there by bioavailability by following polymorphism technique. In this case, alternative polymorphs of different forms may be investigated, and developed four different polymorphs (**Form I, Form II, Form III** and **Form IV)** of Entacapone in different solvents. The prepared polymorphs were characterized by using SEM Analysis, DSC,

XRD and IR spectroscopic methods. It included formulated in to tablets by direct compression method and were evaluated for solubility and dissolution studies. These studies proved that the **Form IV** of Entacapone shown faster rate of dissolution and highest solubility compared to **Form I, Form II, Form III** and pure Entacapone.

2. Materials & Method

Entacapone Pure was obtained from IPCA Laboratories. Bhopal, India. The various solvents used for preparation of crystals were Acetone, Acetonitrile, Acetic acid, Ammonia, Benzene, Chloroform, Di-methyl sulfoxide, (Chempure Laboratories, Chennai).

2.1 Preparation of Crystal Forms from Different Solvents

The drug (0.5g) was dissolved in respective solvents (20ml) to check its solubility. To this solution, another weighed amount of Entacapone (2.5g) was added and refluxed only with Methanol, chloroform, Acetone and Ethylacetate (100ml), for 20 minutes. This solution was filtered through Whatmann filter paper and concentrated by recovery of the solvent to one third of its original volume and kept for crystallization at room temperature to afford well-defined crystals of Entacapone. The crystals obtained were collected by filtration, dried under vacuum for 24 hours and stored in well closed container. The yield was found to be 98%.

2.2 Characterization of crystal forms[5, 6]

2.2.1 Scanning Electron Microscopy

The morphology of each crystalline form was observed by scanning electron microscopy (SEM). A small amount of samples were scattered on double-sided adhesive carbon tabs mounted on SEM stubs and coated with Au/Pd in a Cressington208 sputter coater (Pelco International, Redding, CA). Thereafter, the samples were examined with a JSM-6700F Field Emission SEM (Jeol, Japan) operating at 15 kV.

2.2.2 Differential scanning calorimetry[7]

The instrument was calibrated using Indium as standard. The sample (2-10mg) was weighed accurately in aluminums pan and sealed hermetically using a crimper. Thermo grams were obtained by heating the encapsulated samples at a constant heating rate of 5^{o}C/min with chart speed of 5 mm/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion were determined. The temperature range for the scan was 30^{o}C to 450^{o}C for all the samples.

2.2.3 IR spectroscopy: The crystal samples (2-2.5 mg) were triturated with dried potassium bromide (100 mg) using agate mortar and pestle. These quantities were usually sufficient to give a disc of 13 mm diameter and a spectrum of suitable intensity. The mixture after grinding into a fine powder was spread uniformly in a suitable die and compressed into a pellet form at a pressure of about 10kg/cm^1 for three minutes by using hydraulic press. The resultant pellet was mounted in a suitable holder in the FT-IR spectrophotometer and full range spectra of all crystals were recorded form 4000 cm^{-1} to 400 cm^{-1}.

2.2.4 Powder x-ray diffraction spectroscopy[8]

All crystal samples were ground and screened through 100 meshes. The x-ray diffraction pattern was recorded using Phillips analytical automatic powder diffractometer at 30mA, 40KV. The samples were scanned at a temperature. 25^{0}C at the diffraction angle 2 θ over the range of 5-40 θ.

3. Formulation & Evaluation of Pre, Post Compressional Properties[9]

Selected polymorphs previously passed through 100 mesh were mixed with sufficient quantity of microcrystalline cellulose, sodium starch glycolate, polyvinylpyrrolidone, magnesium stearate and talc by geometrical dilution. The powder mixture was compressed in an electrically driven Tablet punching machine (Cadmach, Ahmadabad) using 9 mm punch to obtain 300mg of tablets and evaluated all the official Pre, Post Compressional Properties of respective tablets according to I.P. These results were shown in Table: 1

Solubility (After 4hrs)	Form - I	Form -II	Form - III	Form -IV	Pure
Absorbance (nm)	0.526	0.688	0.672	0.769	0.402

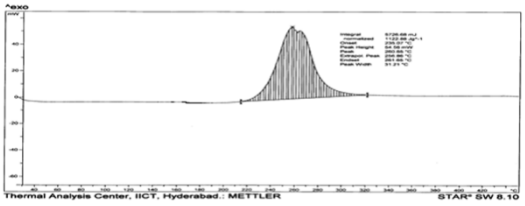
Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	True density (g/ml)
Form-I	299.2 ⊥ 0.15	3.4⊥0.02	4.43+0.25	0.15	140+4	1.0674
Form-II	300 – 1.05	3.3+0.02	4.18±0.06	0.22	110±5	1.0415
Form-III	297.1 ⊥ 1.28	3.4⊥0.02	4.20+0.24	0.13	115+5	1.0507
Form-IV	299.4 + 0.12	3.4+0.01	4.12⊥0.42	0.22	90⊥4	1.0021
Pure	300 ⊥ 0.83	3.3⊥0.01	4.63⊥0.62	0.18	180⊥5	1.0876

4. Results & Discussion

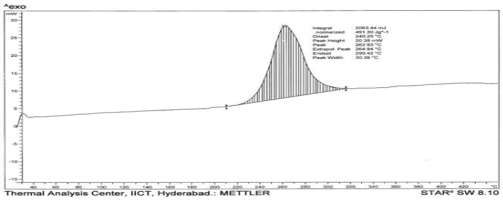
The free base of Pure Entacapone showed appreciable solubility only in chloroform, methanol, acetone & ethyl acetate to be used as solvent for re-crystallization. From DSC data[10], it was observed that the shown spectra are not provided significant variation in between Entacapone-pure and obtained crystal forms i.e., Onset, endset & peak fusion of prepared crystals were similar to Entacapone-pure form shown in figure: I However unlike DSC the SEM Photographs showed a significant variation in their shape between Form-I, Form-IV as well as Entacapone-Pure Form but except Form-II and Form-III shown in Figure: II & Table: II

Figure: I DSC Spectra of Prepared crystal Forms

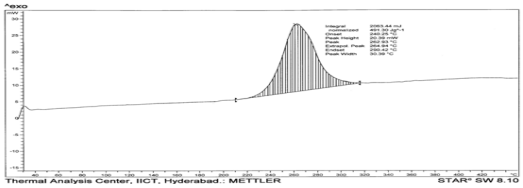
DSC spectra of Form-I



DSC spectra of Form-II



DSC spectra of Form-III



DSC spectra of Form-IV

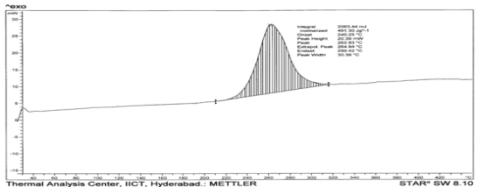


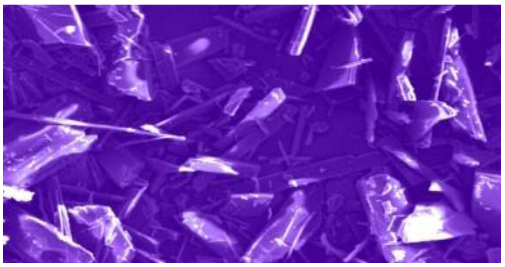
Figure: II SEM Photographs of Prepared Crystal Forms

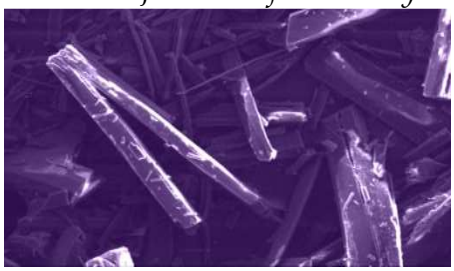
Form-I (Methanol)

Form-II (Chloroform)

Form-III (Acetone)

Form-IV (Ethyl Acetate)

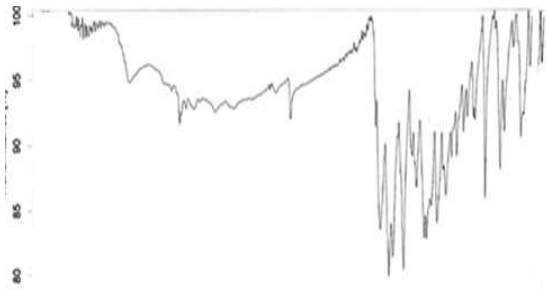




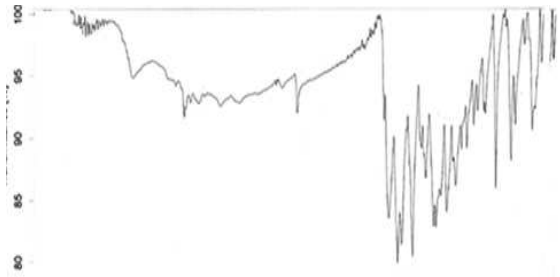
Ir spectra of the Pure drug (Entcapone), prepared crystal (Form-I, Form-II, Form-III and Form-IV) were recorded using potassium bromide disc method in shimatzu FT-IR instrument. It was observed that there was no incompatible reactions/interactions between the drug Entcapone and the solvents used shown in Figure: III

Figure: III Ir comparison spectra of form I to form IV

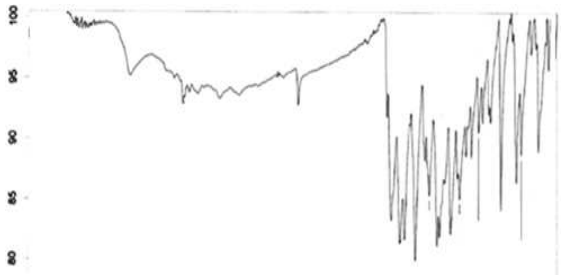
Form-I (Methanol)



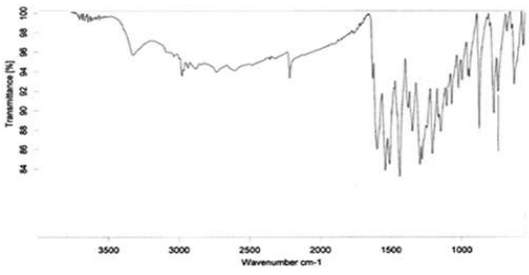
Form-II (Chloroform)



Form-III (Acetone)

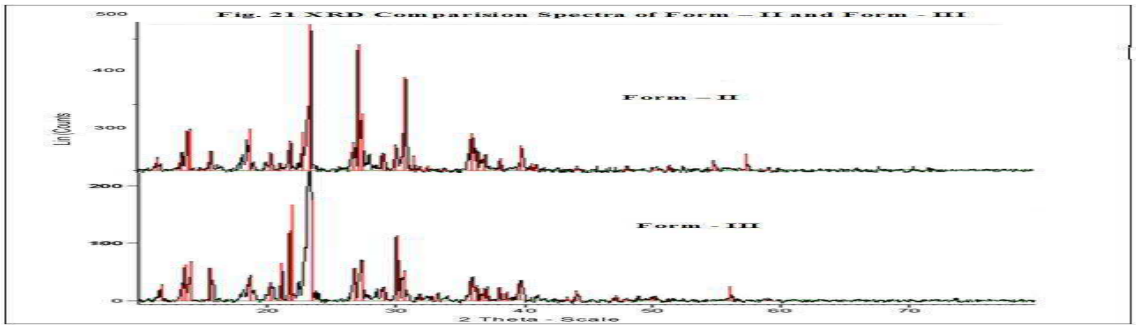


Form-IV (Ethyl acetate)



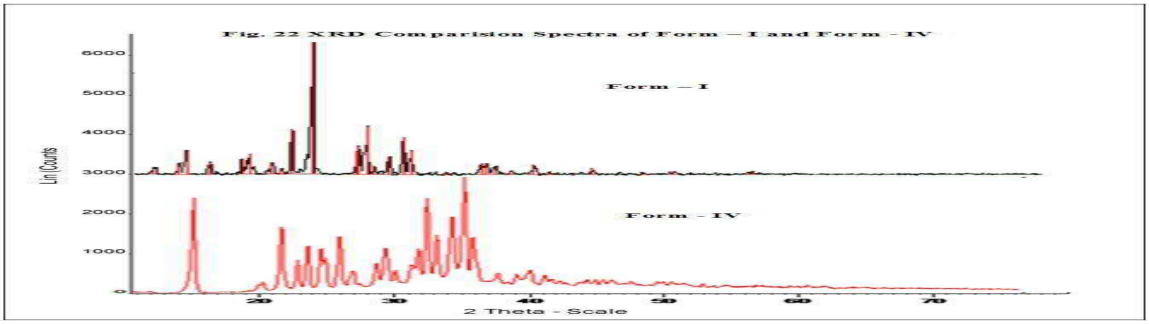
Like SEM the XRD pattern of Form-II (Chloroform) & Form-III (Acetone) was shown Figure: IV, Which shown that the intensity of scattering angle at (23 2θ**)** was same and the main scattering peaks of each from are clustered between 13-30at 2θ angle. So this was evidenced that above two crystal structure were similar expect difference between 31-35 at 2θ.

Figure: IV XRD Comparison Spectra of Form- II & Form- III



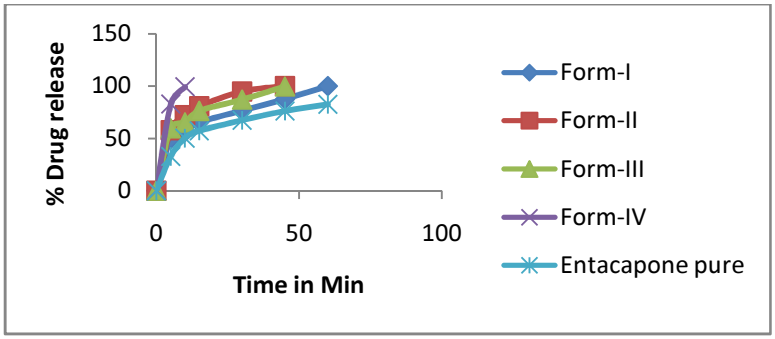
But in case of Figure: V, the XRD pattern of Form-I (Methanol) & Form-IV (Ethyl acetate) was shown the existence of two different crystal structures. This can be easily differentiated from an inspection of the pattern. The most intense peak of Form-I was at 25 2θ but Form-IV was at 28 2θ angle. In these the main scattering peaks of Form-I was between 20-25 2θ and for Form-IV is between 6-30 2θ.

Figure: V XRD Comparison Spectra of Form- I & Form- IV



From the above studies Form-IV has shown the fastest rate of dissolution and highest solubility after 4 hrs compared to Form-I, Form-II, Form-III & Entacapone pure. These results are favored the SEM analysis & XRD results indicating Form-I, IV to be a different crystal habit than Form-II, Form-III & as well as pure Entacapone drug.

Figure: VI Dissolution profile of the tablets prepared from selected crystal forms of Entacapone



5. Summary

The present work was undertaken with the aim to study crystal forms of Entacapone. The objective of the project was to make different crystal forms of Entacapone by crystallization from single solvent method (from Chloroform, Methanol, Acetone, and Ethyl acetate). Efforts were made to characterize the crystalline materials by Melting point, Scanning Electron Microscopy, DSC, FT-IR and XRD. In this characterization melting point or DSC data did not help. But Scanning electron microscopy photographs (Figure: II), XRD spectra of all the crystal forms showed a significant variation in their shape between **Form-I, Form-IV** and **Entacapone pure form.** But except in **Form-II,** Form**-III.** IR spectra of the pure drug (Entacapone) and prepared crystal was given in figure: III. From this it was concluded that there is no incompatible reactions/ interaction between the drug Entacapone and the solvents. These Present polymorphs have shown differences in their dissolution profiles (Figure: VI). Among the four polymorphs **Form-IV** have shown much better dissolution profile indicating that these particular polymorph would show faster bioavailability, which could result in a faster bioactivity.

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